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Roche

ROFERON®-A
(Interferon alfa-2a, recombinant)

Alpha interferons, including Interferon alfa-2a, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping Interferon alfa-2a therapy (see WARNINGS and ADVERSE REACTIONS).

DESCRIPTION: Roferon-A (Interferon alfa-2a, recombinant) is a sterile protein product for use by injection. Roferon-A is manufactured by recombinant DNA technology that employs a genetically engineered *Escherichia coli* bacterium containing DNA that codes for the human protein. Interferon alfa-2a, recombinant is a highly purified protein containing 165 amino acids, and it has an approximate molecular weight of 19,000 daltons. Fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride, 5 mg/L. However, the presence of the antibiotic is not detectable in the final product. Roferon-A is supplied as an injectable solution in a vial or a prefilled syringe. Each glass syringe barrel contains 0.5 mL of product. In addition, there is a needle which is 1/2 inch in length.

Single Use Injectable Solution:

36 million IU (133.3 mcg/mL) Roferon-A per vial — The solution is colorless and each mL contains 36 MIU of Interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate.

Single Use Prefilled Syringes:

3 million IU (111 mcg/0.5 mL) Roferon-A per syringe —The solution is colorless and each 0.5 mL contains 3 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

6 million IU (22.2 mcg/0.5 mL) Roferon-A per syringe — The solution is colorless and each 0.5 mL contains 6 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

9 million IU (33.3 mcg/0.5 mL) Roferon-A per syringe — The solution is colorless and each 0.5 mL contains 9 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

Multidose Injectable Solution:

18 million IU (66.7 mcg/3 mL) Roferon-A per vial — The solution is colorless and each mL contains 6 MIU of Interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate. Each 0.5 mL contains 3 MIU of Interferon alfa-2a, recombinant.

Based on the specific activity of 2.7×10^8IU/mg protein, the corresponding quantities of Interferon alfa-2a, recombinant in the vials described above are approximately 18 MIU (66.7 mcg/3 mL) and 36 MIU (133.3 mcg/mL).

The route of administration for the vial is subcutaneous or intramuscular; the route of administration for the prefilled syringe is subcutaneous only.

CLINICAL PHARMACOLOGY: The mechanism by which Interferon alfa-2a, recombinant, or any other interferon, exerts antitumor or antiviral activity is not clearly understood. However, it is believed that direct antiproliferative action against tumor cells, inhibition of virus replication and modulation of the host immune response play important roles in antitumor and antiviral activity.

The biological activities of Interferon alfa-2a, recombinant are species-restricted, ie, they are expressed in a very limited number of species other than humans. As a consequence, preclinical evaluation of Interferon alfa-2a, recombinant has involved in vitro experiments with human cells and some in vivo experiments.[1] Using human cells in culture, Interferon alfa-2a, recombinant has been shown to have antiproliferative and immunomodulatory activities that are very similar to those of the mixture of interferon alfa subtypes produced by human leukocytes. In vivo, Interferon alfa-2a, recombinant has been shown to inhibit the growth of several human tumors growing in immunocompromised (nude) mice. Because of its species-restricted activity, it has not been possible to demonstrate antitumor activity in immunologically intact syngeneic tumor model systems, where effects on the host immune system would be observable. However, such antitumor activity has been repeatedly demonstrated with, for example, mouse interferon-alfa in transplantable mouse tumor systems. The clinical significance of these findings is unknown.

The metabolism of Interferon alfa-2a, recombinant is consistent with that of alfa interferons in general. Alfa interferons are totally filtered through the glomeruli and undergo rapid proteolytic degradation during tubular reabsorption, rendering a negligible reappearance of intact alfa interferon in the systemic circulation. Small amounts of radiolabeled Interferon alfa-2a, recombinant appear in the urine of isolated rat kidneys, suggesting near complete reabsorption of Interferon alfa-2a, recombinant catabolites. Liver metabolism and subsequent biliary excretion are considered minor pathways of elimination for alfa interferons.

The serum concentrations of Interferon alfa-2a, recombinant reflected a large intersubject variation in both healthy volunteers and patients with disseminated cancer.

In healthy people, Interferon alfa-2a, recombinant exhibited an elimination half-life of 3.7 to 8.5 hours (mean 5.1 hours), volume of distribution at steady-state of 0.223 to 0.748 L/kg (mean 0.400 L/kg) and a total body clearance of 2.14 to 3.62 mL/min/kg (mean 2.79 mL/min/kg) after a 36 MIU (2.2×10^8pg) intravenous infusion. After intramuscular and subcutaneous administrations of 36 MIU, peak serum concentrations ranged from 1500 to 2580 pg/mL (mean 2020 pg/mL) at a mean time to peak of 3.8 hours and from 1250 to 2320 pg/mL (mean 1730 pg/mL) at a mean time to peak of 7.3 hours, respectively. The apparent fraction of the dose absorbed after intramuscular injection was greater than 80%.

The pharmacokinetics of Interferon alfa-2a, recombinant after single intramuscular doses to patients with disseminated cancer were similar to those found in healthy volunteers. Dose proportional increases in serum concentrations were observed after single doses up to 198 MIU. There were no changes in the distribution or elimination of Interferon alfa-2a, recombinant during twice daily (0.5 to 36 MIU), once daily (1 to 54 MIU), or three times weekly (1 to 136 MIU) dosing regimens up to 28 days of dosing. Multiple intramuscular doses of Interferon alfa-2a, recombinant resulted in an accumulation of two to four times the single dose serum concentrations. There is no pharmacokinetic information in patients with chronic hepatitis C, hairy cell leukemia, AIDS-related Kaposi's sarcoma and chronic myelogenous leukemia.

Serum neutralizing activity, determined by a highly sensitive enzyme immunoassay, and a neutralization bioassay, was detected in approximately 25% of all patients who received Roferon-A.[2] Antibodies to human leukocyte interferon may occur spontaneously in certain clinical conditions (cancer, systemic lupus erythematosus, herpes zoster) in patients who have never received exogenous interferon.[3] The significance of the appearance of serum neutralizing activity is not known.

CLINICAL STUDIES: Studies have shown that Roferon-A can normalize serum ALT, improve liver histology and reduce viral load in patients with chronic hepatitis C. Other studies have shown that Roferon-A can produce clinically meaningful tumor regression or disease stabilization in patients with hairy cell leukemia or in patients with AIDS-related Kaposi's sarcoma.[4-6] In Ph-positive Chronic Myelogenous Leukemia, Roferon-A supplemented with intermittent chemotherapy has been shown to prolong overall survival and to delay disease progression compared to patients treated with chemotherapy alone.[7] In addition, Roferon-A has been shown to produce sustained complete cytogenetic responses in a small subset of patients with CML in chronic phase. The activity of Roferon-A in Ph-negative CML has not been determined.

EFFECTS ON CHRONIC HEPATITIS C: The safety and efficacy of Roferon-A was evaluated in multiple clinical trials involving over 2000 patients 18 years of age or older with hepatitis, with or without cirrhosis, who had elevated serum alanine aminotransferase (ALT) levels and tested positive for antibody to hepatitis C. Roferon-A was given three times a week (tiw) by subcutaneous (SC) or intramuscular (IM) injection in a variety of dosing regimens, including dose escalation and de-escalation regimens. Normalization of serum ALT was defined in all studies as two consecutive normal serum ALT values at least 21 days apart. A sustained response (SR) was defined as normalization of ALT both at the end of treatment and at the end of at least 6 months of treatment-free follow-up.

In trials in which Roferon-A was administered for 6 months, 6 MIU, 3 MIU, and 1 MIU were directly compared. Six MIU was associated with higher SR rates but greater toxicity (see ADVERSE REACTIONS). In studies in which the same dose of Roferon-A was administered for 6 or 12 months, the longer duration was associated with higher SR rates and adverse events were no more severe or frequent in the second 6 months than in the first 6 months. Based on these data, the recommended regimens are 3 MIU for 12 months or 6 MIU for the first 3 months followed by 3 MIU for the next 9 months (see Table 1 and DOSAGE AND ADMINISTRATION). There are no direct comparisons of these two regimens.

Younger patients (eg, less than 35 years of age) and patients without cirrhosis on liver biopsy were more likely to respond completely to Roferon-A than those patients greater than 35 years of age or patients with cirrhosis on liver biopsy.

In the two studies in which Roferon-A was administered subcutaneously three times weekly for 12 months, 20/173 (12%) patients experienced a sustained response to therapy (see Table 1). Of these patients, 15/173 (9%) maintained this sustained response during continuous follow-up for up to four years. Patients who have ALT normalization but who fail to have a sustained response following an initial course of therapy may benefit from retreatment with higher doses of Roferon-A (see DOSAGE AND ADMINISTRATION).

A subset of patients had liver biopsies performed both before and after treatment with Roferon-A. An improvement in liver histology as assessed by Knodell Histology Activity Index was generally observed.

A retrospective subgroup analysis of 317 patients from two studies suggested a correlation between improvement in liver histology, durable serum ALT response rates, and decreased viral load as measured by the polymerase chain reaction (PCR).

Table 1.— ALT Normalization in Patients Receiving Therapy With Roferon-A for 12 Months

Study No.	Dose (MIU)	N	End of Treatment [% (95% CI)]	End of Observation (Sustained Response SR) [% (95% CI)]*
1**	3	56	23	11
2	3	117	23	12
1 and 2 Combined	3	173	23 (17-30)	12 (7-17)
3	6-3	210	25 (19-31)	19 (14-25)

*All patients were followed for 6 months after end of treatment.

**EOT and SR rates for Placebo (study 1) were 0.

EFFECTS ON Ph-POSITIVE CHRONIC MYELOGENOUS LEUKEMIA (CML): Roferon-A was evaluated in two trials of patients with chronic phase CML. Study DM84-38 was a single center phase II study conducted at the MD Anderson Cancer Center, which enrolled 91 patients, 81% were previously treated, 82% were Ph positive, and 63% received Roferon-A within 1 year of diagnosis. Study MI400 was a multicenter randomized phase III study conducted in Italy by the Italian Cooperative Study Group on CML in 335 patients; 226 Roferon-A and 109 chemotherapy. Patients with Ph-positive, newly diagnosed or minimally treated CML were randomized (ratio 2:1) to either Roferon-A or conventional chemotherapy with either hydroxyurea or busulfan. In study DM84-38, patients started Roferon-A at 9 MIU/day, whereas in study MI400, it was progressively escalated from 3 to 9 MIU/day over the first month. In both trials, dose escalation for insufficient hematologic response, and dose attenuation or interruption for toxicity was permitted. No formal guidelines for dose attenuation were given in the chemotherapy arm of study MI400. In addition, in the Roferon-A arm, the MI400 protocol allowed the addition of intermittent single agent chemotherapy for insufficient hematologic response to Roferon-A alone. In this trial, 44% of the Roferon-A treated patients also received intermittent single agent chemotherapy at some time during the study.

The two studies were analyzed according to uniform response criteria. For hematologic response: complete response (WBC <9×10^9/L, normalization of the differential with no immature forms in the peripheral blood, disappearance of splenomegaly), partial response (>50% decrease from baseline of WBC to <$20\% \times 10^9$/L). For cytogenetic response: complete response (0% Ph-positive metaphases), partial response (1% to 34% Ph-positive metaphases).

In study DM84-38, the median survival from initiation of Roferon-A was 47 months. In study MI400, the median survival for the patients on the interferon arm was 69 months, which was significantly better than the 55 months seen in the chemotherapy control group (48 patients in study MI400 proceeded to BMT and in study DM84-38, 15 patients proceeded to BMT). Roferon-A treatment significantly delayed disease progression to blastic phase as evidenced by a median time to disease progression of 69 months to 46 months with chemotherapy.

By multivariate analysis of prognostic factors associated with all 335 patients entered into the randomized study, treatment with Roferon-A (with or without intermittent additional chemotherapy; p=0.006), Sokal index[8] (p=0.006) and WBC (p=0.023) were the three variables associated with an improved survival, independent of other baseline characteristics (Karnofsky performance status and hemoglobin being the other factors entered into the model).

In study MI400, overall hematologic responses, [complete responses (CR) and partial responses (PR)], were observed in approximately 60% of patients treated with Roferon-A (40% CR, 20% PR), compared to 70% with chemotherapy (30% CR, 40% PR). The median time to reach a complete hematologic response was 5 months in the Roferon-A arm and 4 months in the chemotherapy arm. The overall cytogenetic response rate (CR+PR), in patients receiving Roferon-A, was 10% and 12% in studies MI400 and DM84-38, respectively, according to the intent-to-treat principle. In contrast, only 2% of the patients in the chemotherapy arm of study MI400 achieved a cytogenetic response (with no complete responses). Cytogenetic responses were observed only in patients who had complete hematologic responses. In study DM84-38, hematologic and cytogenetic response rates were higher in the subset of patients treated with Roferon-A within 1 year of diagnosis (76% and 17%, respectively) compared to the subset initiating Roferon-A therapy more than 1 year from diagnosis (29% and 4%, respectively). In an exploratory analysis, patients who achieved a cytogenetic response lived longer than those who did not.

Severe adverse events were observed in 66% and 31% of patients on study DM84-38 and MI400, respectively. Dose reduction and temporary cessation of therapy was required frequently. Permanent cessation of Roferon-A, due to intolerable side effects, was required in 15% and 23% of patients on studies DM84-38 and MI400, respectively (see ADVERSE REACTIONS).

Limited data are available on the use of Roferon-A in children with Ph-positive, adult-type CML. A published report on 15 children with CML suggests a safety profile similar to that seen in adult CML; clinical responses were also observed[9] (see DOSAGE AND ADMINISTRATION).

EFFECTS ON HAIRY CELL LEUKEMIA: A multicenter US phase II study (N2752) enrolled 218 patients; 75 were evaluable for efficacy in a preliminary analysis; 218 patients were evaluable for safety. Patients were to receive a starting dose of Roferon-A up to 6 MIU/m²/day, for an induction period of 4 to 6 months. Responding patients were to receive 12 months maintenance therapy.

During the first 1 to 2 months of treatment of patients with hairy cell leukemia, significant depression of hematopoiesis was likely to occur. Subsequently, there was improvement in circulating blood cell counts. Of the 75 patients who were evaluable for efficacy following at least 16 weeks of therapy, 46 (61%) achieved complete or partial response. Twenty-one patients (28%) had a minor remission, 8 (11%) remained stable, and none had worsening of disease. All patients who achieved either a complete or partial response had complete or partial normalization of all peripheral blood elements including hemoglobin level, white blood cell, neutrophil, monocyte and platelet counts with a concomitant decrease in peripheral blood and bone marrow hairy cells. Responding patients also exhibited a marked reduction in red blood cell and platelet transfusion requirements, a decrease in infectious episodes and improvement in performance status. The probability of survival for 2 years in patients receiving Roferon-A (94%) was statistically increased compared to a historical control group (75%).

EFFECTS ON AIDS-RELATED KAPOSI'S SARCOMA: In six studies with Roferon-A, doses of 3 to 54 MIU daily were evaluated for the treatment of AIDS-related Kaposi's sarcoma in more than 350 patients. Four dosage regimens of Roferon-A were evaluated for initial induction. Thirty-nine patients received 3 MIU daily; 99 patients received an escalating regimen of 3 MIU, 9 MIU and 18 MIU each daily for 3 days, followed by 36 MIU daily; 119 patients received 36 MIU daily; and 16 patients received doses greater than 36 MIU to a maximum of 54 MIU daily. An additional 91 patients received Roferon-A in combination with vinblastine. The best response rate associated with acceptable toxicity was observed when Roferon-A was administered as a single agent at a dose of 36 MIU daily. The escalating regimen of 3 to 36 MIU daily provided equivalent therapeutic benefit with some amelioration of acute toxicity in some patients. In AIDS-related Kaposi's sarcoma, lower doses were less effective in inducing tumor regression and doses higher than 36 MIU daily were associated with unacceptable toxicity.

As summarized in Table 2, the likelihood of response to Roferon-A varied with the clinical manifestations of human immunodeficiency virus (HIV) infection. Patients with prior opportunistic infection or B symptoms are unlikely to respond to treatment with Roferon-A.

Table 2.— Likelihood of Response to Roferon-A in Patients With AIDS-Related Kaposi's Sarcoma

	$CD_4(T_4)$ Lymphocyte Count	Objective Response Rate (%)		
No. Pts.*	(cells/mm³)	CR	PR	Total
83	0-200	3.6	3.6	7.2
51	201-400	15.7	11.8	27.5
33	>400	24.2	21.2	45.4

In the 28 patients evaluated who had prior opportunistic infection or B symptoms, the response rate was 3.6%.

*Patients had no prior opportunistic infection or B symptoms. B symptoms include night sweats, weight loss of greater than 10% of body weight or 15 lbs, or fever greater than 100°F without an identifiable source of infection.

Patients who were otherwise asymptomatic, with no prior opportunistic infection and near-normal levels of CD_4 lymphocytes, experienced higher response rates. Responding patients with a baseline CD_4 lymphocyte count greater than 200 cells/mm³ had a distinct survival advantage over both responding patients with a baseline CD_4 lymphocyte count of 200 cells/mm³ or less and non-responding patients regardless of their baseline CD_4 lymphocyte count. Median survival for responding patients with CD_4 lymphocyte counts of greater than 200 to 400 cells/mm³ had not been reached but was greater than 32.7 months from the initiation of therapy. For responding patients with CD_4 lymphocyte counts of greater than 400 cells/mm³, the median survival had not been reached but was greater than 29.5 months.

A classification system for staging AIDS-related Kaposi's sarcoma has been described based on location and extent of disease. In studies of Roferon-A, no difference was noted in response rates for patients with different stages of Kaposi's sarcoma. Likelihood of response was related to manifestations of HIV infection (baseline CD_4 lymphocyte count, prior opportunistic infection or B symptoms) and not to extent of tumor involvement. The median time to response was 2.7 months. The median duration of response for patients achieving a partial or complete response was 6.3 and 20.7 months, respectively. Complete and partial responses lasting in excess of 3 years have been observed. Therapy was discontinued because of progression of Kaposi's sarcoma, development of severe opportunistic infection or severe adverse effects. The median time to discontinuation of treatment was 12.5 months for responding patients and 2.3 months for patients who did not respond.

INDICATIONS AND USAGE: Roferon-A is indicated for the treatment of chronic hepatitis C, hairy cell leukemia and AIDS-related Kaposi's sarcoma in patients 18 years of age or older. In addition, it is indicated for chronic phase, Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of diagnosis).

FOR PATIENTS WITH CHRONIC HEPATITIS C: Roferon-A is indicated for use in patients with chronic hepatitis C diagnosed by HCV antibody and/or a history of exposure to hepatitis C who have compensated liver disease and are 18 years of age or older. A liver biopsy and a serum test for the presence of antibody to HCV should be performed to establish the diagnosis of chronic hepatitis C. Other causes of hepatitis, including hepatitis B, should be excluded prior to therapy with Roferon-A.

FOR PATIENTS WITH AIDS-RELATED KAPOSI'S SARCOMA: Roferon-A is indicated for the treatment of AIDS-related Kaposi's sarcoma in a select group of patients. In determining whether a patient should be treated, the physician should assess the likelihood of response based on the clinical manifestations of HIV infection, including prior opportunistic infections, presence of B symptoms, and CD_4 count, and the manifestations of Kaposi's sarcoma requiring treatment (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS: Roferon-A is contraindicated in patients with known hypersensitivity to alfa interferon or any component of the product. The injectable solutions contain benzyl alcohol and are contraindicated in any individual with a known allergy to that preservative.

WARNINGS: Roferon-A should be administered under the guidance of a qualified physician (see DOSAGE AND ADMINISTRATION). Appropriate management of the therapy and its complications is possible only when adequate facilities are readily available.

DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL IDEATION, SUICIDAL ATTEMPTS AND SUICIDES HAVE BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH ALFA INTERFERONS, INCLUDING ROFERON-A. Patients to be treated with Roferon-A should be informed that depression and suicidal ideation may be side effects of treatment and should be advised to report these side effects immediately to the prescribing physician. Patients receiving Roferon-A therapy should receive close monitoring for the occurrence of depressive symptomatology. Cessation of treatment should be considered for patients experiencing depression. Although dose reduction or treatment cessation may lead to resolution of the depressive symptomatology, depression may persist and suicides have occurred after withdrawing therapy (see PRECAUTIONS and ADVERSE REACTIONS).

Central nervous system adverse reactions have been reported in a number of patients. These reactions included decreased mental status, dizziness, impaired memory, agitation, manic behavior and psychotic reactions. More severe obtundation and coma have been rarely observed. Most of these abnormalities were mild and reversible within a few days to 3 weeks upon dose reduction or discontinuation of Roferon-A therapy. Careful periodic neuropsychiatric monitoring of all patients is recommended.

Roferon-A should be used with caution in patients with severe preexisting cardiac disease, severe renal or hepatic disease, seizure disorders and/or compromised central nervous system function.

Roferon-A should be administered with caution to patients with cardiac disease or with any history of cardiac illness. Acute, self-limited toxicities (ie, fever, chills) frequently associated with Roferon-A administration may exacerbate preexisting cardiac conditions. Rarely, myocardial infarction has occurred in patients receiving Roferon-A. Cases of cardiomyopathy have been observed on rare occasions in patients treated with alfa interferons.

Patients with a history of autoimmune hepatitis or a history of autoimmune disease and patients who are immunosuppressed transplant recipients should not be treated with Roferon-A. Controlled studies of Roferon-A therapy in patients with advanced cirrhosis and/or decompensated liver disease have not been performed. In chronic hepatitis C, initiation of alfa-interferon therapy, including Roferon-A, has been reported to cause transient liver abnormalities, which in patients with poorly compensated liver disease can result in increased ascites, hepatic failure or death.

Leukopenia and elevation of hepatic enzymes occurred frequently but were rarely dose-limiting. Thrombocytopenia occurred less frequently. Proteinuria and increased cells in urinary sediment were also seen infrequently. Dose-limiting hepatic or renal toxicities were unusual. Infrequently, severe renal toxicities, sometimes requiring renal dialysis, have been reported with alfa-interferon therapy alone or in combination with IL-2 (see PRECAUTIONS).

Infrequently, severe or fatal gastrointestinal hemorrhage has been reported in association with alfa-interferon therapy.

Alpha interferons suppress bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pretreatment and monitored routinely during therapy. Alpha interferon therapy should be discontinued in patients who develop severe decreases in neutrophil (<0.5×10^9/L) or platelet counts (<25×10^9/L).

Caution should be exercised when administering Roferon-A to patients with myelosuppression or when Roferon-A is used in combination with other agents that are known to cause myelosuppression. Synergistic toxicity has been observed when Roferon-A is administered in combination with zidovudine (AZT).[10] The effects of Roferon-A when combined with other drugs used in the treatment of AIDS-related disease are not known.

Hyperglycemia has been observed rarely in patients treated with Roferon-A. Symptomatic patients should have their blood glucose measured and followed-up accordingly. Patients with diabetes mellitus may require adjustment of their anti-diabetic regimen.

Roferon-A should not be used for the treatment of visceral AIDS-related Kaposi's sarcoma associated with rapidly progressive or life-threatening disease.

The injectable solutions contain benzyl alcohol and should not be used by patients with a known allergy to benzyl alcohol. This product is not indicated for use in neonates or infants and should not be used by patients in that age group. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol. There have been reports of permanent neuropsychiatric deficits and multiple system organ failure associated with benzyl alcohol in neonates and infants. The amount of benzyl alcohol at which toxicity or adverse effects may occur in neonates or infants is not known (see CONTRAINDICATIONS).

Ophthalmologic Disorders: Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema are induced or aggravated by treatment with Interferon alfa-2a or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (eg, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Interferon alfa-2a treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

PRECAUTIONS: *General:* In all instances where the use of Roferon-A is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of Roferon-A therapy should be carried out with caution and with adequate consideration of the further need for the drug and, alertness to possible recurrence of toxicity. The minimum effective doses of Roferon-A for treatment of hairy cell leukemia, AIDS-related Kaposi's sarcoma and chronic myelogenous leukemia have not been established.

Variations in dosage and adverse reactions exist among different brands of Interferon. Therefore, do not use different brands of Interferon in a single treatment regimen.

Rare cases of autoimmune diseases including thrombocytopenia, vasculitis, Raynaud's phenomenon, rheumatoid arthritis, lupus erythematosus, and rhabdomyolysis have been observed in patients treated with alpha interferons. Any patient developing an autoimmune disorder during treatment should be closely monitored and, if appropriate, treatment should be discontinued.

Information for Patient: Patients should be cautioned not to change brands of Interferon without medical consultation, as a change in dosage may result. Patients should be informed regarding the potential benefits and risks attendant to the use of Roferon-A. If home use is determined to be desirable by the physician, instructions on appropriate use should be given, including review of the contents of the enclosed Patient Information Sheet. Patients should be well hydrated, especially during the initial stages of treatment.

Patients should be thoroughly instructed in the importance of proper disposal procedures and cautioned against reusing syringes and needles. If home use is prescribed, a puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient. The full container should be disposed of according to directions provided by the physician.

Patients receiving high-dose alfa interferon should be cautioned against performing tasks that require complete mental alertness such as operating machinery or driving a motor vehicle. Patients to be treated with Roferon-A should be informed that depression and suicidal ideation may be side effects of treatment and should be advised to report these side effects immediately to the prescribing physician.

Laboratory Tests: Complete blood with differential platelet counts and clinical chemistry tests should be performed before initiation of Roferon-A therapy and at appropriate periods during therapy. Since responses of hairy cell leukemia, AIDS-related Kaposi's sarcoma, chronic hepatitis C and chronic myelogenous leukemia are not generally observed for 1 to 3 months after initiation of treatment, very careful monitoring for severe depression of blood cell counts is warranted during the initial phase of treatment.

Those patients who have preexisting cardiac abnormalities and/or are in advanced stages of cancer should have electrocardiograms taken before and during the course of treatment.

For patients being treated for chronic hepatitis C, serum ALT should be evaluated before therapy to establish baselines and repeated at week 2 and monthly thereafter following initiation of therapy for monitoring clinical response. Patients with neutrophil count <1500/mm³, platelet count <75,000/mm³, hemoglobin <10 g/dL and creatinine >1.5 mg/dL were excluded from several major chronic hepatitis C studies; patients with these laboratory abnormalities should be carefully monitored if treated with Roferon-A.

Patients with preexisting thyroid abnormalities may be treated if normal thyroid stimulating hormone (TSH) levels can be maintained by medication. Testing of TSH levels in these patients is recommended at baseline and every 3 months following initiation of therapy.

Drug Interactions: Roferon-A has been reported to reduce the clearance of theophylline.[11,12] The clinical relevance of this interaction is presently unknown. Interactions between Roferon-A and other drugs have not been fully evaluated. Caution should be exercised when administering Roferon-A in combination with other potentially myelosuppressive agents (see WARNINGS).

Other Drug Interactions: Alfa interferons may affect the oxidative metabolic process by reducing the activity of hepatic microsomal cytochrome enzymes in the P450 group. Although the clinical relevance is still unclear, this should be taken into account when prescribing concomitant therapy with drugs metabolized by this route.

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The neurotoxic, hematotoxic or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons. Interactions could occur following concurrent administration of centrally acting drugs. Use of Roferon-A in conjunction with interleukin-2 may potentiate risks of renal failure.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Roferon-A has not been tested for its carcinogenic potential.

Mutagenesis: A. Internal Studies — Ames tests using six different tester strains, with and without metabolic activation, were performed with Roferon-A up to a concentration of 1920 µg/plate. There was no evidence of mutagenicity.

Human lymphocyte cultures were treated in vitro with Roferon-A at noncytotoxic concentrations. No increase in the incidence of chromosomal damage was noted.

B. Published Studies — There are no published studies on the mutagenic potential of Roferon-A. However, a number of studies on the genotoxicity of human leukocyte interferon have been reported.

A chromosomal defect following the addition of human leukocyte interferon to lymphocyte cultures from a patient suffering from a lymphoproliferative disorder has been reported.

In contrast, other studies have failed to detect chromosomal abnormalities following treatment of lymphocyte cultures from healthy volunteers with human leukocyte interferon.

It has also been shown that human leukocyte interferon protects primary chick embryo fibroblasts from chromosomal aberrations produced by gamma rays.

Impairment of Fertility: Roferon-A has been studied for its effect on fertility in Macaca mulatta (rhesus monkeys). Nonpregnant rhesus females treated with Roferon-A at doses of 5 and 25 MIU/kg/day have shown menstrual cycle irregularities, including prolonged or shortened menstrual periods and erratic bleeding; these cycles were considered to be anovulatory on the basis that reduced progesterone levels were noted and that expected increases in preovulatory estrogen and luteinizing hormones were not observed. These monkeys returned to a normal menstrual rhythm following discontinuation of treatment.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Roferon-A has been shown to demonstrate a statistically significant increase in abortifacient activity in rhesus monkeys when given at approximately 20 to 500 times the human dose. A study in pregnant rhesus monkeys treated with 1, 5 or 25 MIU/kg/day of Roferon-A in their early to midfetal period (days 22 to 70 of gestation) has failed to demonstrate teratogenic activity for Roferon-A.

There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects: Dose-related abortifacient activity was observed in pregnant rhesus monkeys treated with 1, 5 or 25 MIU/kg/day of Roferon-A in their early to midfetal period (days 22 to 70 of gestation). A late fetal period study (days 79 to 100 of gestation) is in progress and as yet there have been no reports of any increased rate of abortion.

Usage in Pregnancy: Safe use in human pregnancy has not been established. Therefore, Roferon-A should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Information from primate studies showed dose-related menstrual irregularities and an increased incidence of spontaneous abortions. Decreases in serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.[13] Therefore, fertile women should not receive Roferon-A unless they are using effective contraception during the therapy period.

The injectable solution contains benzyl alcohol. The excipient benzyl alcohol can be transmitted via the placenta. The possibility of toxicity should be taken into account in premature infants after the administration of Roferon-A solution for injection immediately prior to birth or Cesarean section.

Male fertility and teratologic evaluations have yielded no significant adverse effects to date.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Roferon-A, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Use of Roferon-A in children with Ph-positive adult-type CML is supported by evidence from adequate and well-controlled studies of Roferon-A in adults with additional data from the literature on the use of alfa interferon in children with CML. A published report on 15 children with Ph-positive adult-type CML suggests a safety profile similar to that seen in adult CML; clinical responses were also observed[9] (see DOSAGE AND ADMINISTRATION).

For all other indications, safety and effectiveness have not been established in patients below the age of 18 years.

The injectable solutions are not indicated for use in neonates or infants and should not be used by patients in that age group. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol (see WARNINGS).

ADVERSE REACTIONS: Depressive illness and suicidal behavior, including suicidal ideation and suicides, have been reported in association with the use of alfa-interferon products. The incidence of reported depression has varied substantially among trials, possibly related to the underlying disease, dose, duration of therapy and degree of monitoring, but has been reported to be 15% or higher (see WARNINGS).

FOR PATIENTS WITH CHRONIC HEPATITIS C: The most frequent adverse experiences were reported to be possibly or probably related to therapy with 3 MIU tiw Roferon-A, were mostly mild to moderate in severity and manageable without the need for discontinuation of therapy. A relative increase in the incidence, severity and seriousness of adverse events was observed in patients receiving doses above 3 MIU tiw.

Adverse reactions associated with the 3 MIU dose include:

Flu-like Symptoms: Fatigue (58%), myalgia/arthralgia (51%), flu-like symptoms (33%), fever (28%), chills (23%), asthenia (6%), sweating (5%), leg cramps (3%) and malaise (1%).

Central and Peripheral Nervous System: Headache (52%), dizziness (13%), paresthesia (7%), confusion (7%), concentration impaired (4%) and change in taste or smell (3%).

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Gastrointestinal: Nausea/vomiting (33%), diarrhea (20%), anorexia (14%), abdominal pain (12%), flatulence (3%), liver pain (3%), digestion impaired (2%) and gingival bleeding (2%).

Psychiatric: Depression (16%), irritability (15%), insomnia (14%), anxiety (5%) and behavior disturbances (3%).

Pulmonary and Cardiovascular: Dryness or inflammation of oropharynx (6%), epistaxis (4%), rhinitis (3%), arrhythmia (1%) and sinusitis (<1%).

Skin: Injection site reaction (29%), partial alopecia (19%), rash (8%), dry skin or pruritus (7%), hematoma (1%), psoriasis (<1%), cutaneous eruptions (<1%), eczema (<1%) and seborrhea (<1%).

Other: Conjunctivitis (4%), menstrual irregularity (2%) and visual acuity decreased (<1%).

Patients receiving 6 MIU tiw experienced a higher incidence of severe psychiatric events (9%) than those receiving 3 MIU tiw (6%) in two large US studies. In addition, more patients withdrew from these studies when receiving 6 MIU tiw (11%) than when receiving 3 MIU tiw (7%). Up to half of patients receiving 3 MIU or 6 MIU tiw withdrawing from the study experienced depression or other psychiatric adverse events. At higher doses anxiety, sleep disorders, and irritability were observed more frequently. An increased incidence of fatigue, myalgia/arthralgia, headache, fever, chills, alopecia, sleep disturbances and dry skin or pruritus was also generally observed during treatment with higher doses of Roferon-A.

Generally there were fewer adverse events reported in the second 6 months of treatment than in the first 6 months for patients treated with 3 MIU tiw. Patients tolerant of initial therapy with Roferon-A generally tolerate re-treatment at the same dose, but tend to experience more adverse reactions at higher doses.

Infrequent adverse events (>1% but <3% incidence) included: cold feeling, cough, muscle cramps, diaphoresis, dyspnea, eye pain, reactivation of herpes simplex, lethargy, edema, sexual dysfunction, shaking, skin lesions, stomatitis, tooth disorder, urinary tract infection, weakness in extremities.

FOR PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA:

For patients with chronic myelogenous leukemia, the percentage of adverse events, whether related to drug therapy or not, experienced by patients treated with rIFNα-2a is given below. Severe adverse events were observed in 66% and 31% of patients on study DM84-38 and MI400, respectively. Dose reduction and temporary cessation of therapy were required frequently. Permanent cessation of Roferon-A, due to intolerable side effects, was required in 15% and 23% of patients on studies DM84-38 and MI400, respectively.

Flu-like Symptoms: Fever (92%), asthenia or fatigue (88%), myalgia (68%), chills (63%), arthralgia/bone pain (47%) and headache (44%).

Gastrointestinal: Anorexia (48%), nausea/vomiting (37 %) and diarrhea (37%).

Central and Peripheral Nervous System: Headache (44%), depression (28%), decreased mental status (16%), dizziness (11%), sleep disturbances (11%), paresthesia (8%), involuntary movements (7%) and visual disturbance (6%).

Pulmonary and Cardiovascular: Coughing (19%), dyspnea (8%) and dysrhythmia (7%).

Skin: Hair changes (including alopecia) (18%), skin rash (18%), sweating (15%), dry skin (7%) and pruritus (7%).

Uncommon adverse events (< 4%) reported in clinical studies included chest pain, syncope, hypotension, impotence, alterations in taste or hearing, confusion, seizures, memory loss, disturbances of libido, bruising and coagulopathy. Miscellaneous adverse events that were rarely observed included Coombs' positive hemolytic anemia, aplastic anemia, hypothyroidism, cardiomyopathy, hypertriglyceridemia and bronchospasm.

FOR PATIENTS WITH HAIRY CELL LEUKEMIA:

Constitutional (100%): Fever (92%), fatigue (86%), headache (64%), chills (64%), weight loss (33%), dizziness (21%) and flu-like symptoms (16%).

Integumentary (79%): Skin rash (44%), diaphoresis (22%), partial alopecia (17%), dry skin (17%) and pruritus (13%).

Musculoskeletal (73%): Myalgia (71%), joint or bone pain (25%) and arthritis or polyarthritis (5%).

Gastrointestinal (69%): Anorexia (43%), nausea/vomiting (39%) and diarrhea (34%).

Head and Neck (45%): Throat irritation (21%), rhinorrhea (12%) and sinusitis (11%).

Pulmonary (40%): Coughing (16%), dyspnea (12%) and pneumonia (11%).

Central Nervous System (39%): Dizziness (21%), depression (16%), sleep disturbance (10%), decreased mental status (10%), anxiety (6%), lethargy (6%), visual disturbance (6%) and confusion (5%).

Cardiovascular (39%): Chest pain (11%), edema (11%) and hypertension (11%).

Pain (34%): Pain (24%) and pain in back (16%).

Peripheral Nervous System (23%): Paresthesia (12%) and numbness (12%).

Rarely (<5%), central nervous system effects including gait disturbance, nervousness, syncope and vertigo, as well as cardiac adverse events including murmur, thrombophlebitis and hypotension were reported. Adverse experiences that occurred rarely, and may have been related to underlying disease, included ecchymosis, epistaxis, bleeding gums and petechiae. Urticaria and inflammation at the site of injection were also rarely observed.

FOR PATIENTS WITH AIDS-RELATED KAPOSI'S SARCOMA:

Flu-like Symptoms: Fatigue (95%), fever (74%), myalgia (69%), headache (66%), chills (41%) and arthralgia (24%).

Gastrointestinal: Anorexia (65%), nausea (51%), diarrhea (42%), emesis (17%) and abdominal pain (15%).

Central and Peripheral Nervous System: Dizziness (40%), decreased mental status (17%), depression (16%), paresthesia (8%), confusion (8%), diaphoresis (7%), visual disturbances (5%), sleep disturbances (5%) and numbness (3%).

Pulmonary and Cardiovascular: Coughing (27%), dyspnea (11%), edema (9%), chest pain (4%) and hypotension (4%).

Skin: Partial alopecia (22%), rash (11%) and dry skin or pruritus (5%).

Other: Weight loss (25%), change in taste (25%), dryness or inflammation of the oropharynx (14%), night sweats (8%) and rhinorrhea (4%).

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Occasionally (<3%) nervous system effects including anxiety, nervousness, emotional lability, vertigo and forgetfulness, as well as cardiac adverse events, including palpitations and arrhythmia, were reported. Other adverse experiences that occurred occasionally (<3%) and may have been related to underlying disease, included sinusitis, constipation, chest congestion, pneumonia, urticaria and flatulence. Adverse experiences which occurred rarely (<1%) included ataxia, seizures, cyanosis, gastric distress, bronchospasm, pain at injection site, earache, eye irritation and rhinitis. Miscellaneous adverse experiences such as poor coordination, lethargy, muscle contractions, neuropathy, tremor, involuntary movement, syncope, aphasia, aphonia, dysarthria, amnesia, weakness and flushing of skin were observed in less than 0.5% of patients. Cases of cardiomyopathy have been observed on rare occasions in patients treated with alfa interferons.

IN OTHER INVESTIGATIONAL STUDIES OF ROFERON-A:

The following infrequent adverse events have been reported in one or more of the approved clinical indications as well as with the investigational use of Roferon-A (<5%): pancreatitis, colitis, gastrointestinal hemorrhage, stomatitis, thyroid dysfunction (including hypothyroidism and hyperthyroidism), diabetes (in some patients requiring insulin therapy), and pneumonitis (some cases responding to interferon cessation and corticosteroid therapy). In addition to the adverse experiences noted above, other adverse experiences that occurred included: abdominal fullness, hypermotility, hepatitis, gait disturbance, hallucinations, encephalopathy, psychomotor retardation, coma, stroke, transient ischemic attacks, dysphasia, sedation, apathy, irritability, hyperactivity, claustrophobia, loss of libido, congestive heart failure, myocardial infarction, Raynaud's phenomenon, hot flashes, tachypnea, ischemic retinopathy, excessive salivation and anaphylactic reactions. These adverse experiences occurred rarely (<1%).

The following events have been rarely observed (<3%) in some patients receiving Roferon-A: autoimmune diseases, ie, vasculitis, arthritis, hemolytic anemia and lupus erythematosus syndrome. The mechanism by which these events develop and their relationship to Roferon-A therapy are unclear. Similar events have been reported for other types of interferon.

ABNORMAL LABORATORY TEST VALUES: The percentage of patients with chronic hepatitis C, hairy cell leukemia, with AIDS-related Kaposi's sarcoma, and with chronic myelogenous leukemia who experienced a significant abnormal laboratory test value *(NCI or WHO grades III or IV)* at least once during their treatment with Roferon-A is shown in the following table:

Table 3. — Significant Abnormal Laboratory Test Values

	Chronic Hepatitis C (n=203) 3 MIU tiw	Chronic Myelogenous Leukemia‡ US Study (n=91)	Chronic Myelogenous Leukemia‡ Non-US Study (n=219)	Hairy Cell Leukemia (n=218)	AIDS-related Kaposi's Sarcoma (n=241)
Leukopenia	1.5%	20%	3%	45%*	49%
Neutropenia	10%	22%	0%	68%*	52%
Thrombocytopenia	4.5%	27%	5%	62%*	35%
Anemia (Hb)	0%	15%	4%	31%*	27%
SGOT	NAP	5%	1%	9%	46%
Alk. Phosphatase	0%	3%	1%	3%	11%
LDH	NAP	NA	NA	<1%	10%
Proteinuria	0%	NA	NA	10%†	<1%

*In the majority of patients, initial hematologic laboratory test values were abnormal due to their underlying disease.
†Ten percent of the patients experienced a proteinuria >1+ at least once.
‡Patients enrolled in the two clinical studies receiving at least one dose of Roferon-A.
NAP=Not applicable.
NA = Not assessed.

CHRONIC HEPATITIS C: The incidence of neutropenia *(WHO grades III or IV)* was over twice as high in those treated with 6 MIU tiw (21%) as those treated with 3 MIU tiw (10%).

CHRONIC MYELOGENOUS LEUKEMIA: In the two clinical studies, a severe or life-threatening anemia was seen in up to 15% of patients. A severe or life-threatening leukopenia and thrombocytopenia were observed in up to 20% and 27% of patients, respectively. Changes were usually reversible when therapy was discontinued. One case of aplastic anemia and one case of Coombs' positive hemolytic anemia were seen in 310 patients treated with rIFNα-2a in clinical studies. Severe cytopenias led to discontinuation of therapy in 4% of all Roferon-A treated patients.

Transient increases in liver transaminases or alkaline phosphatase of any intensity were seen in up to 50% of patients during treatment with Roferon-A. Only 5% of patients had a severe or life-threatening increase in SGOT. In the clinical studies, such abnormalities required termination of therapy in less than 1% of patients.

HAIRY CELL LEUKEMIA: Increases in serum phosphorus (≥ 1.6 mmol/L) and serum uric acid (≥ 9.1 mg/dL) were observed in 9% and 10% of patients, respectively. The increase in serum uric acid is likely to be related to the underlying disease. Decreases in serum calcium (≤ 1.9 mmol/L) and serum phosphorus (≤ 0.9 mmol/L) were seen in 28% and 22% of patients, respectively.

OVERDOSAGE: There are no reports of overdosage, but repeated large doses of interferon can be associated with profound lethargy, fatigue, prostration, and coma. Such patients should be hospitalized for observation and appropriate supportive treatment given.

DOSAGE AND ADMINISTRATION: Roferon-A recommended dosing regimens are different for each of the following indications as described below.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

Roferon-A vials are administered either subcutaneously or intramuscularly. The Roferon-A prefilled syringe is administered subcutaneously only, due to the length of the syringe needle (1/2 inch) provided in the packaging.

CHRONIC HEPATITIS C: The recommended dosage of Roferon-A for the treatment of chronic hepatitis C is 3 MIU three times a week (tiw) administered subcutaneously or intramuscularly for 12 months (48 to 52 weeks). As an alternative, patients may be treated with an induction dose of 6 MIU tiw for the first 3 months (12 weeks) followed by 3 MIU tiw for 9 months (36 weeks). Normalization of serum ALT generally occurs within a few weeks after initiation of treatment in responders. Approximately 90% of patients who respond to Roferon-A do so within the first 3 months of treatment; however, patients responding to Roferon-A with a reduction in ALT should complete 12 months of treatment. Patients who have no

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response to Roferon-A within the first 3 months of therapy are not likely to respond with continued treatment; treatment discontinuation should be considered in these patients.

Patients who tolerate and partially or completely respond to therapy with Roferon-A but relapse following its discontinuation may be re-treated. Re-treatment with either 3 MIU tiw or with 6 MIU tiw for 6 to 12 months may be considered. Please see ADVERSE REACTIONS regarding the increased frequency of adverse reactions associated with treatment with higher doses.

Temporary dose reduction by 50% is recommended in patients who do not tolerate the prescribed dose. If adverse events resolve, treatment with the original prescribed dose can be re-initiated. In patients who cannot tolerate the reduced dose, cessation of therapy, at least temporarily, is recommended.

CHRONIC MYELOGENOUS LEUKEMIA: For patients with Ph-positive CML in chronic phase: Prior to initiation of therapy, a diagnosis of Philadelphia chromosome positive CML in chronic phase by the appropriate peripheral blood, bone marrow and other diagnostic testing should be made. Monitoring of hematologic parameters should be done regularly (eg, monthly). Since significant cytogenetic changes are not readily apparent until after hematologic response has occurred, and usually not until several months of therapy have elapsed, cytogenetic monitoring may be performed at less frequent intervals. Achievement of complete cytogenetic response has been observed up to 2 years following the start of Roferon-A treatment.

The recommended initial dose of Roferon-A is 9 MIU daily administered as a subcutaneous or intramuscular injection. Based on clinical experience,[3] short-term tolerance may be improved by gradually increasing the dose of Roferon-A over the first week of administration from 3 MIU daily for 3 days to 6 MIU daily for 3 days to the target dose of 9 MIU daily for the duration of the treatment period.

The optimal dose and duration of therapy have not yet been determined. Even though the median time to achieve a complete hematologic response was 5 months in study MI400, hematologic responses have been observed up to 18 months after treatment start. Treatment should be continued until disease progression. If severe side effects occur, a treatment interruption or a reduction in either the dose or the frequency of injections may be necessary to achieve the individual maximally tolerated dose (see PRECAUTIONS).

Limited data are available on the use of Roferon-A in children with CML. In one report of 15 children with Ph-positive, adult-type CML doses between 2.5 to 5 MIU/m²/day given intramuscularly were tolerated.[9] In another study, severe adverse effects including deaths were noted in children with previously untreated, Ph-negative, juvenile CML, who received interferon doses of 30 MIU/m²/day.[14]

HAIRY CELL LEUKEMIA: Prior to initiation of therapy, tests should be performed to quantitate peripheral blood hemoglobin, platelets, granulocytes and hairy cells and bone marrow hairy cells. These parameters should be monitored periodically (eg, monthly) during treatment to determine whether response to treatment has occurred. If a patient does not respond within 6 months, treatment should be discontinued. If a response to treatment does occur, treatment should be continued until no further improvement is observed and these laboratory parameters have been stable for about 3 months. Patients with hairy cell leukemia have been treated for up to 24 consecutive months. The optimal duration of treatment for this disease has not been determined.

The induction dose of Roferon-A is 3 MIU daily for 16 to 24 weeks, administered as a subcutaneous or intramuscular injection. Subcutaneous administration is particularly suggested for, but not limited to, thrombocytopenic patients (platelet count <50,000) or for patients at risk for bleeding. The recommended maintenance dose is 3 MIU, three times a week (tiw). Dose reduction by one-half or withholding of individual doses may be needed when severe adverse reactions occur. The use of doses higher than 3 MIU is not recommended in hairy cell leukemia.

AIDS-RELATED KAPOSI'S SARCOMA: Roferon-A is useful for the treatment of AIDS-related Kaposi's sarcoma in a select group of patients. In determining whether a patient should be treated, the physician should assess the likelihood of response based on the clinical manifestations of HIV infection and the manifestations of Kaposi's sarcoma requiring treatment (see CLINICAL PHARMACOLOGY).

Indicator lesion measurements and total lesion count should be performed before initiation of therapy. These parameters should be monitored periodically (eg, monthly) during treatment to determine whether response to treatment or disease stabilization has occurred. When disease stabilization or a response to treatment occurs, treatment should continue until there is no further evidence of tumor or until discontinuation is required because of a severe opportunistic infection or adverse effects. The optimal duration of treatment for this disease has not been determined.

The recommended induction dose of Roferon-A is 36 MIU daily for 10 to 12 weeks, administered as an intramuscular or subcutaneous injection. Subcutaneous administration is particularly suggested for, but not limited to, patients who are thrombocytopenic (platelet count <50,000) or who are at risk for bleeding. The recommended maintenance dose is 36 MIU, three times a week (tiw). If severe reactions occur, the dose should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. An escalating schedule of 3 MIU, 9 MIU and 18 MIU each daily for 3 days followed by 36 MIU daily for the remainder of the 10- to 12-week induction period has also produced equivalent therapeutic benefit with some amelioration of the acute toxicity in some patients.

HOW SUPPLIED:

Single Use Injectable Solution: (for subcutaneous or intramuscular administration)

36 million IU Roferon-A per vial — Each 1 mL contains 36 MIU of Interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate. Boxes of 1 (NDC 0004-2012-09).

Single Use Prefilled Syringes: (for subcutaneous administration only)

3 million IU Roferon-A per syringe — Each 0.5 mL contains 3 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate. Boxes of 1 (NDC 0004-2015-09); Boxes of 6 (NDC 0004-2015-07).

6 million IU Roferon-A per syringe — Each 0.5 mL contains 6 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate. Boxes of 1 (NDC 0004-2016-09); Boxes of 6 (NDC 0004-2016-07).

9 million IU Roferon-A per syringe — Each 0.5 mL contains 9 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate. Boxes of 1 (NDC 0004-2017-09); Boxes of 6 (NDC 0004-2017-07).

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Multidose Injectable Solution: (for subcutaneous or intramuscular administration)

18 million IU Roferon-A per vial — Each 1 mL contains 6 MIU of Interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate. Each 0.5 mL contains 3 MIU of Interferon alfa-2a, recombinant. Once the vial is entered, it must be used within 30 days. The 18 MIU multidose vial contains an average of 22.8 MIU of Interferon alfa-2a, recombinant in order to provide the delivery of six 0.5 mL doses, each containing 3 MIU of Roferon-A Interferon alfa-2a, recombinant for injection. Boxes of 1 (NDC 0004-2011-09).

Storage: The injectable solution and the prefilled syringe should be stored in the refrigerator at 36° to 46°F (2° to 8°C). Do *not* freeze or shake.

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